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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/308,830	08/04/99	SCHLIEVERT	P 600.346USWO

HM12/0118

MERCHANT & GOULD
3100 NORWEST CENTER
90 SOUTH SEVENTH STREET
MINNEAPOLIS MN 55402-4131

EXAMINER	
LEE, L	
ART UNIT	**PAPER NUMBER**
1645	9

DATE MAILED: 01/18/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/308,830	Applicant(s) Schllevert et al
	Examiner LIL e	Group Art Unit 1645

☒ Responsive to communication(s) filed on *Dec 6, 1999*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-18* is/are pending in the applicat

Of the above, claim(s) *15 and 16* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-14, 17, and 18* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *7*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Application No.: 09/308,830

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [X] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [ ] 7. Other: _____

Applicant Must Provide:

- [X] An initial ~~or substitute~~ computer readable form (CRF) copy of the "Sequence Listing".
- [ ] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE

DETAILED ACTION

Election/Restriction

1. Applicant's election without traverse of group I, claims 1-14 and 17-18 in Paper No. 8 is acknowledged.

Nucleotide and /or Amino acid Sequence Disclosures

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

There is no SEQ ID NO for the sequence disclosed on page 54 and there is no CRF disc for the listed sequences.

Information Disclosure Statement

3. Items listed on form PTO-1449 filed on Nov 24, 1999 have be considered by the examiner.

Drawings

4. This application has been filed with informal drawings which are acceptable for examination purposes only. The drawings are objected to by the draftsperson under 37 C.R.F. 1.84 or 1.152. See PTO-948 for details. Correction of the noted defects can be deferred until the application is allowed by the examiner.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-14 and 17-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 1-14 and 17-18 are vague and indefinite for using the terms "mutant SPE-A toxin", "fragment thereof", and "wild type SPE-A toxin" because there is no defined specific structure or characteristics in the claims. Without reciting a specific protein sequence or characteristics for the mutant toxin, a fragment, and the wild type SPE-A toxin, one of ordinary skill in the art would not be reasonably be apprised of the metes and bounds of the claimed subject matter. Claims 1-14 and 17-18 are further vague and indefinite for recitation of the positions of substituted amino acid in the mutant SPE-A toxin, such as "in N-terminal alpha helix 3, ... or is a cysteine" in claim 2, and the numbered amino acids in claims 3-11. Since there is no specific structure and amino acid sequence recited in the claims one skilled in the art can not locate the positions of the substituted amino acids in the mutant SPE-A toxin. The term "substantially nonlethal", "substantially corresponding", "substantially enhance", and "comparable to" in claim 1 and 12, respectively, is a relative term which renders the claims indefinite. The terms "substantially nonlethal", "substantially corresponding", "substantially

enhance", and "comparable to" are not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-4, 6, 8, 10, 12-14, and 17-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for single, double, and triple mutant of speA toxin, N20D, C87S, C90S, K157E, S195A, K16N, D45N, N20D/C98S, N20D/K157E, AND N20D/D45N/C98S, respectively, and the method for protecting an animal or reducing symptoms administering the mutants, does not reasonably provide enablement for any mutant of speA toxin or other toxin which is substantially nonlethal compared with any protein substantially corresponding to wild type speA toxin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

As to claims 1-4, 6, 8, 10, 12-14, and 17-18, the claims are drawn to and encompass any mutant of speA toxin or any mutant combinations up to six point mutations in a single toxin protein or in any toxin which is substantially nonlethal compared with any protein substantially corresponding to wild type speA toxin because the specification defines that a mutant speA toxin is a toxin having at least one change in a amino acid compared with a protein substantially corresponding to wild type speA toxin and a wild type speA toxin includes variants of a wild

type speA toxin and these speA toxins may have different amino acid or their genes may have a different nucleotide sequence from shown in Figure 3 with same biological activity (page 9).

However, the specification only teaches the mutations of N20D, C87S, C90S, K157E, S195A, K16N, D45N, N20D/C98S, N20D/K157E, and N20D/D45N/C98S, respectively, in speA toxin cloned and sequenced by Johnson et al (1984) and Weeks et al (1986) (see specification, page 4) and the maximum substitution in a single polypeptide is only up to three amino acids, specifically N20D/D45N/C98S. The specification fails to provide guidance as to any other amino acid substitution in speA toxin cloned and sequenced by Johnson et al (1984) and Weeks et al (1986) or any amino acid substitution in any other toxin other than the speA toxin or a substitution being more than three amino acids in a single protein toxin. Protein chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted a *priori* and must be determined empirically on a case by case basis (Rudinger et al., in "Peptide Hormones", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a protein leads to unpredictable change in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic

activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3):1247-1252, 1988). Moreover, Kline et al teach that a point mutation can even enhance the toxicity of a wild type SPE-A toxin (Infection and Immunity 64 (3), 861-869, Mar 1996 in Form 1449). These reference demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity of a protein. Therefore, without specifically reciting position, combinations of the point mutations, and specific amino acid change, one skilled in the art would be forced to randomly altering amino acid in a toxin and randomly combine different combinations of the mutations which would lead to unpredictable results regarding the functional activity of the protein toxins. Therefore, the skilled artisan could not make and use the invention without undue experimentation as is broadly claimed.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 1-2, 12-14, and 17-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Hartwing et al (International Immunology 5 (8), 869-875, 19993 in Form 1449).

Claims 1-2, 12-14, and 17-18 are drawn to a mutant SPE-A toxin or fragment being substantially nonlethal and a method for protecting animal against at least one biological activity

of wild type SPE-A or reducing symptoms associated with toxic shock administering the mutant toxin.

Hartwing et al teach several mutants Streptococcal pyrogenic exotoxin A (SPEA) at different positions of SPEA (page 872, Figure 2) and the method for protecting animal against biological activity of wild type SPEA (Methods, Induction of neutralizing antibodies).

12. Claims 1-2, and 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Kaller et al. (J Exp Med 175:387, Feb 1992 in Form 1449).

Kaller et al teach Streptococcal enterotoxin B mutants which stimulated all of the T cell hybridoms poorly in comparison with the wild type toxin indicating the substantially nonlethal property (Results).

13. Claims 1-3, 6, 8, and 12-14 and 17-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Okonogi et al (US 4,172,126, Oct 23, 1979).

Okonogi et al teach a Streptococcus toxin inactived by persimmon tannin treatment, which is substantially nonlethal in comparison with the wild type toxin and the inactived toxin can protect the challenged animal (Example 2).

14. Claims 1-6, 8-10, and 12-14 are rejected under 35 U.S.C. 102(a) as being anticipated by Kline et al (Infection and Immunity 64 (3), 861-869, Mar 1996 in Form 1449).

Kline et al teach several mutants Streptococcal pyrogenic exotoxin A (SPEA) at different positions of SPEA including N20A, D45A, and C98S (Figure 4), which are substantially nonlethal in comparison with the wild type toxin.

Double Patenting

15. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

16. Claim 2 is provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 1 of copending Application No. 08/973,391.

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 1, 3-14, and 17-18 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11, 14-19, 22-23 of copending Application No. 08/973391. Although the conflicting claims are not identical, they

are not patentably distinct from each other because claims 1-11, 14-19, 22-23 of copending Application No. 08/973391 are the obvious variations of the claims 1, 3-14, and 17-18 in the instant application as listed below:

Claims 1, 12, 13, 14 of the instant application to claims 1, 9-11, 16-19 of copending Application No. 08/973,391;

Claim 3 of the instant application to claim 2 of copending Application No. 08/973,391;

Claim 4 of the instant application to claim 3 of copending Application No. 08/973,391;

Claim 5 of the instant application to claim 4 of copending Application No. 08/973,391;

Claim 6 of the instant application to claim 5 of copending Application No. 08/973,391;

Claim 7 of the instant application to claim 6 of copending Application No. 08/973,391;

Claim 8 of the instant application to claim 7 of copending Application No. 08/973,391;

Claim 9 of the instant application to claim 8 of copending Application No. 08/973,391;

Claims 17, 18 of the instant application to claims 14-15, 22-23 of copending Application No. 08/973,391; respectively.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Status of Claims

19. No claims are allowed. All claims stand rejected. Claims 7 and 11 are free of prior art.

Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1645 by facsimile transmission. The faxing of such papers must conform with the notice

published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Li Lee, M.D., Ph.D. whose telephone number is (703) 308-8891. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995.

Li Lee, M.D., Ph.D.
January 12, 2000

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600